Clinical Pearls and Pitfalls

Pearls and pitfalls: Adverse cutaneous reactions after COVID-19 vaccination

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ABSTRACT

Background: *Rashes after coronavirus disease of 2019 (COVID-19) mRNA vaccinations occur with typical and atypical presentations.*

Objective: *The goal of this article is to increase awareness and review the various diagnosis and management of cutaneous adverse reactions associated with COVID-19 vaccinations for allergy/immunology fellows, residents, general physicians, and general practitioners.*

Methods: *Pertinent information was included from the patient's case. A review of the available literature using the works cited in the most up-to-date reviews was completed.*

Results: *A case of a patient with cutaneous adverse reaction after COVID-19 vaccination as presented, followed by a review of cutaneous reactions after COVID-19 vaccinations.*

Conclusion: *Providers should be aware of the different rashes after COVID-19 vaccinations. Pearls and pitfalls of the diagnosis and management are provided.*

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Question:

A 12-year-old healthy boy presented to the allergy clinic for evaluation of a rash that occurred 5 days after his first dose of the coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) (Pfizer, New York, NY, USA/BioN-Tech, Mainz, Germany). The patient first saw a rash on his right hand (Fig. 1). More lesions subsequently occurred on his back, legs, chest, and abdomen along skin tension lines (Figs. 2 and 3). There was no indication of mucosal involvement, fever, joint pain, respiratory symptoms, or a history of reactions to previous vaccinations. No other members of the household displayed similar skin findings. Topical diphenhydramine, 1% hydrocortisone cream, and oral cetirizine had been tried with minimal improvement. What is the best next step in management?

A. Obtain severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and human herpesvirus (HHV) 6/7 serologies.
B. Provide reassurance, symptomatic management, and recommend the second vaccination at the appropriate time interval.
C. Provide reassurance and recommend the second vaccination after the rash has resolved.
D. Provide symptomatic management and SARS-CoV2 serologies to determine the need for a second vaccination.
E. Refer to dermatologist for a biopsy to confirm the diagnosis and then consider a second vaccination at the appropriate time interval.

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INTRODUCTION

Several skin conditions have been associated with both COVID-19 infection and COVID-19 mRNA vaccinations.[1–13] Adverse cutaneous reactions after COVID-19 vaccinations include local injection site reactions, immediate reactions, delayed reactions, reactions secondary to viral reactivation, and autoimmune reactions as well as various miscellaneous cutaneous reactions. Most cutaneous reactions occurred in women (84%) and middle-aged people after the first dose of vaccine, with the onset of reactions ranging from 1 to 21 days after vaccination.

Figure 1. *Annular erythematous plaque on the right hand.*

CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

Local Injection Site Reactions

Local injection site reactions occur minutes to days after COVID-19 vaccinations and present with erythema, edema, induration, pruritus, and pain at the injection site.[2] These symptoms typically resolve within a few days and are more commonly seen in patients < 60 years of age.[2]

Immediate Reactions

Immediate or immunoglobulin E (IgE) mediated (type I hypersensitivity) reactions to COVID-19 vaccines present with urticaria, angioedema, or anaphylaxis. Despite an initial focus on polyethylene glycol or cross-reactive polysorbate 80, the allergen responsible for these reactions has not been determined and non–IgE-mediated mast cell degranulation may be involved.[2,3,14] Urticaria, pruritus, and angioedema within 4 hours of vaccination are common among the IgE-mediated generalized cutaneous reactions.[3]

Figure 2. *discrete, numerous, mildly erythematous papules on the chest.*

Figure 3. *Scattered skin colored to erythematous 2-mm to 1.5-cm papules and plaques of the trunk, extremities, and face sparing the palms and soles along skin tension lines in a "Christmas tree" pattern.*

Delayed Reactions

Delayed large local reactions may occur within 1 week of vaccination and most often with COVID-19 mRNA vaccinations.[2,3] Erythema multiforme can also occur after mRNA vaccinations.[3] Urticaria can also be delayed, may occur up to 14 days after vaccination, and can be augmented by coincidental use of nonsteroidal anti-inflammatory drugs.[2,3,5] Morbilliform and pruritic maculopapular reactions can also occur.[2,3] Fixed drug eruptions have also been reported, although these are usually associated with drugs rather than induced by vaccines.[6,7] Vaccine-related eruptions of papules and plaques range from small papules (mild), erythematous scaly papules, and plaques that resemble pityriasis rosea (PR) like changes (moderate), to edematous and crusted papules

(robust).[4] Acute generalized exanthematous pustulosis occurred in one patient, with fever and an acute pruritic nonfollicular pustular eruption that involved her skin folds ~5 days after her first dose of Pfizer vaccine.[7] Steven-Johnson syndrome has also been reported.[5]

Virus Reactivation

As described in this case, PR is a benign papulosquamous eruption distributed on the trunk and extremities that can start as a single, oval lesion, called a "herald patch," on the trunk, followed by centrifugal spread along skin tension lines in a classic "Christmas tree" pattern.[1,8] PR lesions resolve spontaneously over a 6–8-week period.[9] Recent reports related to cutaneous reactions associated with both COVID-19 infection and vaccination during the pandemic show a slight increase in PR cases possibly related to HHV-6 reactivation.[1,8,10] One suggested mechanism for vaccine-induced PR-like reactions (or moderate vaccine-induced PR-like reactions) is immune dysregulation due to a $CD4^+$ T-cell–mediated skin reaction in which the vaccine distracts the immune system's control of latent HHV6/7, which allows for reactivation.[1,8,11]

Herpes zoster caused by reactivation of the varicella-zoster virus can occur after COVID-19 vaccinations.[2,3,5] Herpes zoster is characterized by multiple, painful, possibly itchy vesicular or ulcerative lesions that occur along a dermatomal distribution but can progress systemically in individuals who are immunocompromised.[12] Possible mechanisms include a COVID-19 infection or vaccination related lymphopenia and subsequent decreased cell-mediated immunity, which allows for reactivation of varicella-zoster virus.[12]

Autoimmune Reactions

Infections and vaccines can trigger new or exacerbate existing autoimmune conditions.[2] Vaccine-induced thrombotic thrombocytopenia can also be associated with a clinical syndrome characterized by cerebral venous sinus thrombosis and/or splanchnic venous thrombosis after virus vector–based COVID-19 vaccinations.[2] Vaccine-induced immune thrombocytopenia presents with purpura and bleeding possibly due to autoimmune responses against platelets.[2]

Other Miscellaneous Reactions

Erythema and erythematous macular rashes, chilblain or pseudo-chilblain like rashes, lymphomatoid drug eruption that resemble PLEVA (pityriasis pichenoides et varioliformis acute), erythema nodosum, late-onset atopic dermatitis, annular lichen planus, and erythema nodosum have been reported in the literature with temporal association of up to 10 days within a COVID-19 vaccination.[5,6]

DIAGNOSIS

Most cutaneous reactions can be diagnosed based on their clinical morphology and temporal relationship to vaccination. Although it is possible to obtain serology for SARS-CoV-2 as well as HHV-6 serology to confirm a suspected diagnosis for PR, it is not necessary.[1,8,11] Polymerase chain reaction tests on a vesical sample of herpes zoster with concerning rashes can be obtained to confirm a diagnosis.[12] A biopsy can be helpful when the diagnosis is uncertain.[2]

MANAGEMENT

Most delayed reactions that occur after COVID-19 vaccination are benign and resolve within a week of presentation.[2] For type I hypersensitivity reactions to vaccination, evaluation by an allergist/immunologist is appropriate to identify possible allergens and for administration of subsequent vaccination doses.[2] Most patients who experience adverse cutaneous reactions and even anaphylaxis with the first dose can tolerate the second dose of COVID-19 vaccination with a rare recurrence of symptoms.[3–5,7,15–17] Severe cutaneous adverse reactions such as Steven Johnson Syndrome are absolute contraindications to a second vaccination.[4]

The treatments for rashes after COVID-19 reactions vary from observation to symptomatic treatment with antihistamine, topical or oral steroids, or antivirals.[7] Urticaria can be managed symptomatically with antihistamines and is not a contraindication for future vaccinations. Delayed large local reactions are managed symptomatically and do not preclude future vaccinations.[2] Several treatment options besides "watchful waiting" have been proposed to treat PR and PR-like reactions, including oral antihistamines, oral corticosteroids, oral antivirals, and macrolide antibiotics.[8,12] Most of these reactions are self-limiting and delay of a second vaccination is not recommended.[1,6–8]

Specifically for the management of this case, the patient was seen by a dermatologist who diagnosed PR based on the clinical presentation. No serologic studies were obtained given the presentation. The patient used oral antihistamines as needed and was encouraged to obtain his second vaccine. His symptoms resolved after 6 weeks, which followed the typical course of PR.[9] Despite repeated discussions and reassurance, the parent declined getting his second vaccination due to children bullying the patient about his rash. This example highlights the psychological impact rashes after a COVID-19 vaccination can have on patients, which may lead to vaccine hesitancy.[17–19] This underscores the importance of continued investigation, compassion, and counseling with assisting

patients through the potential adverse effects of COVID-19 vaccinations.[17–19]

CONCLUSION

There are many cutaneous reactions that can occur after COVID-19 vaccinations. Allergists should be aware of the various self-limited cutaneous reactions associated with a COVID-19 vaccine reaction, provide symptomatic treatment, and, in the majority of cases, recommend future vaccinations except for rare and severe conditions.[1,2,5,8]

Correct Answer:

A. Incorrect. Obtaining SARS-CoV2 and HHV6/7 serologies are not required to diagnose and manage PR.
B. Correct. PR and PR-like reactions are benign conditions associated with HHV6/7 but do not require biopsy or serologies to confirm. Providing reassurance, symptomatic management, and recommending the second vaccination at the appropriate time interval are correct.
C. Incorrect. Although providing reassurance and symptomatic management are appropriate, vaccinations should not be delayed.
D. Incorrect. The patient will require a second vaccination regardless of the SARS-CoV2 titers.
E. Incorrect. Although referral to a dermatologist can be helpful nebulous diagnosis, biopsy is not required to diagnose PR or PR-like reactions.

Pearls

- There are several different types of rashes that can occur after COVID-19 mRNA vaccination and can be identified based on clinical assessment.
- PR has been described in numerous case reports after COVID-19 vaccination and can have a classic or atypical clinical presentation.

Pitfalls

- Most cutaneous reactions are diagnosed clinically without serologies or biopsies unless the diagnosis is uncertain.
- Most skin rashes after COVID-19 mRNA vaccination are self-limiting and should not delay future vaccination series.

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